How Vaccines are Developed and Tested & Post Approval Safety Assessment

Development and testing cycle of a vaccine

North Carolina Immunization Conference -
Juggling the Complexities of Immunization
Greensboro, NC
August 1, 2013

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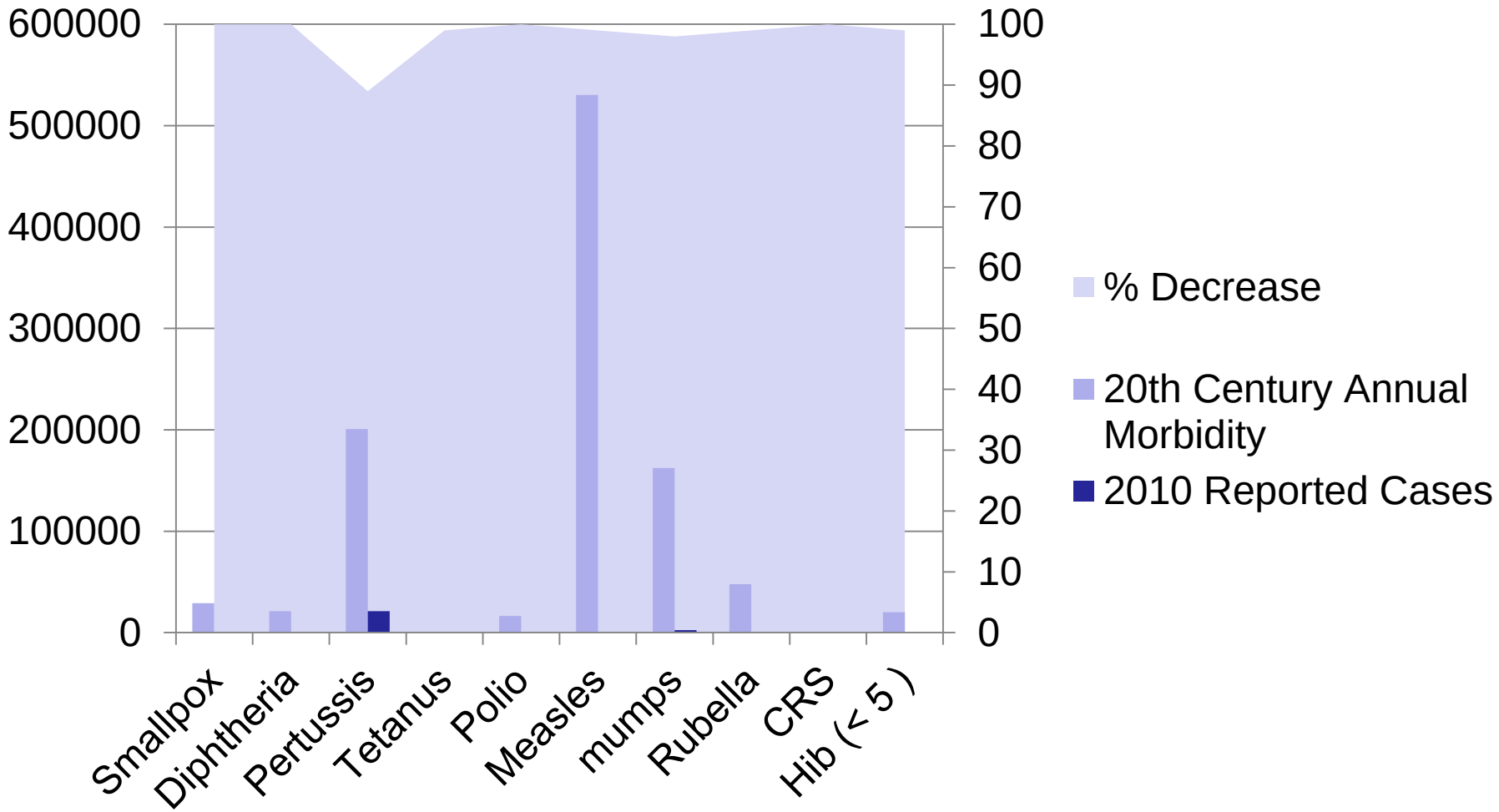
Objectives

- Describe vaccine oversight to ensure vaccine safety
- Discuss avenues to report vaccine adverse events.

Impact of Vaccines: Comparison of 20th Century Annual Morbidity and Current Morbidity



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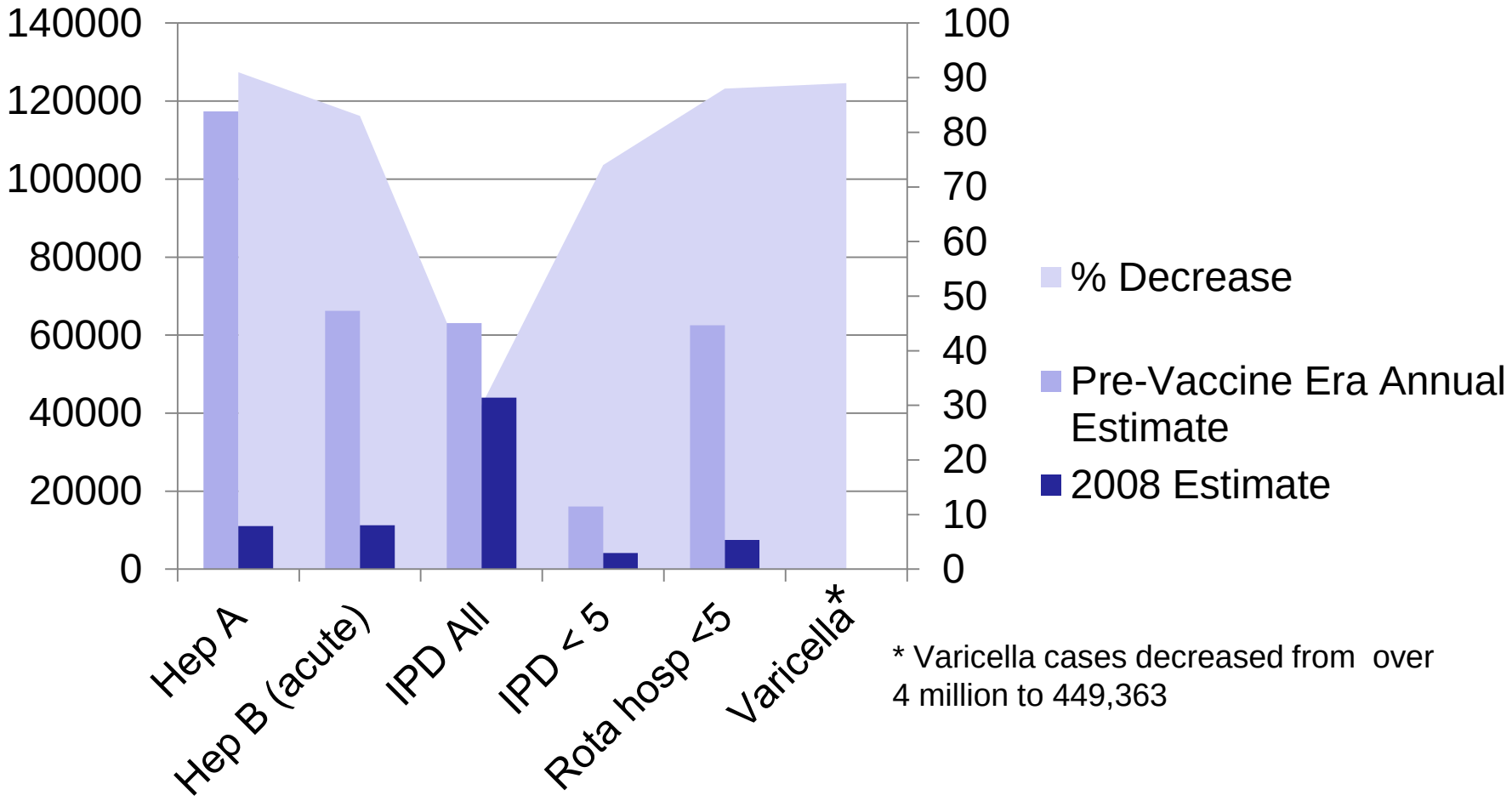
Adapted from Centers For Disease Control And Prevention. Epidemiology And Prevention Of Vaccine-preventable Diseases. Atkinson W, Wolfe S, Hamborsky J, Eds. 12th Ed., Second Printing. Washington DC: Public Health Foundation, 2012.

Impact of Vaccines: Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate



* Varicella cases decreased from over 4 million to 449,363

Adapted from Centers For Disease Control And Prevention. Epidemiology And Prevention Of Vaccine-preventable Diseases. Atkinson W, Wolfe S, Hamborsky J, Eds. 12th Ed., Second Printing. Washington DC: Public Health Foundation, 2012.

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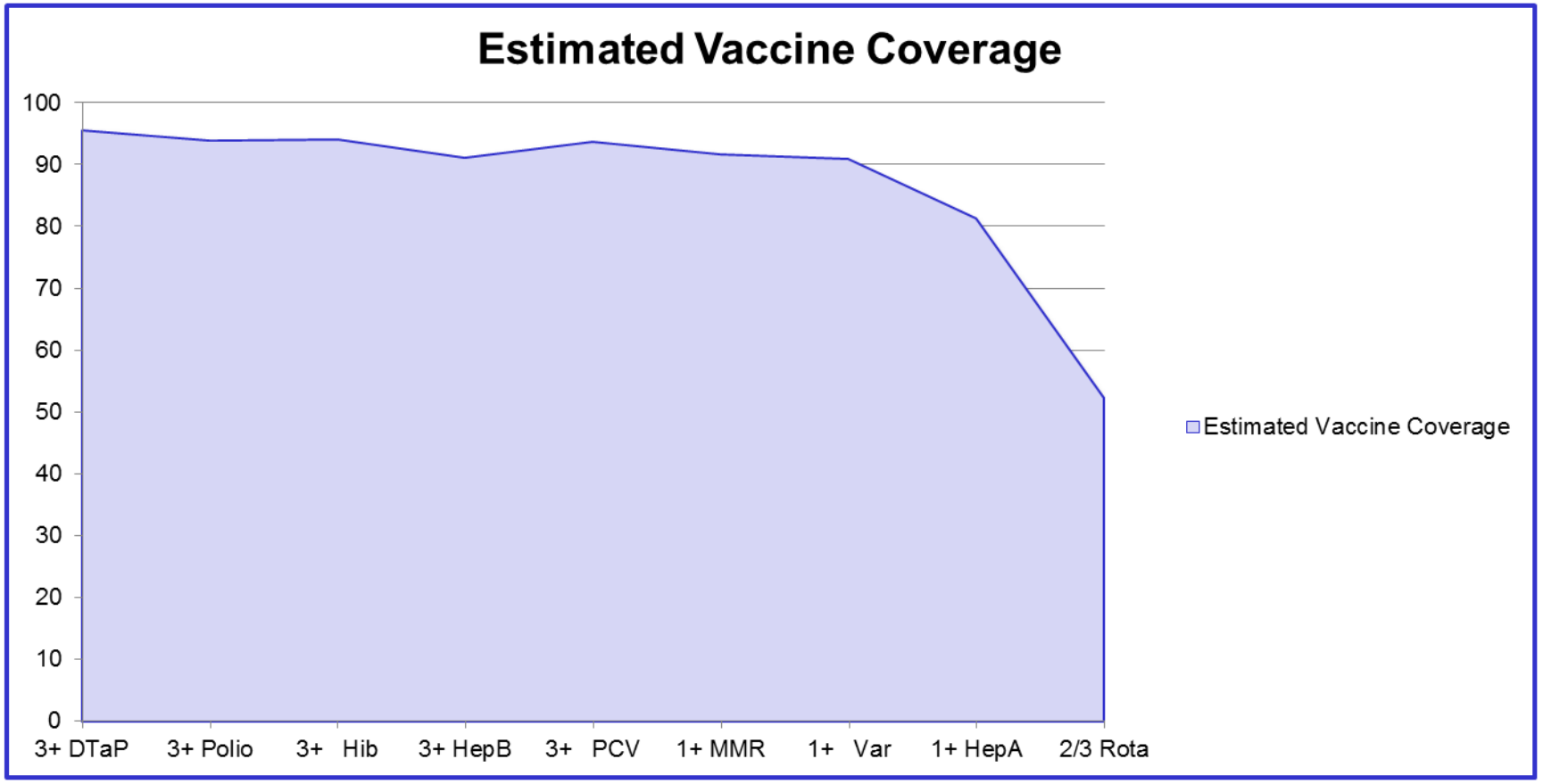
Importance of Vaccine Safety

- No medical intervention is 100% safe
- Vaccines are given to healthy individuals so low tolerance for risk
  - Compare to therapeutic interventions there is tolerance for risk
- Vaccines are given to virtually everyone starting in the newborn period
  - Safety problems could potentially have an impact on a large number of persons

Estimated Vaccine Coverage with Individual Vaccines and Selected Vaccine Series Among Children 19-35 Months of Age in The US



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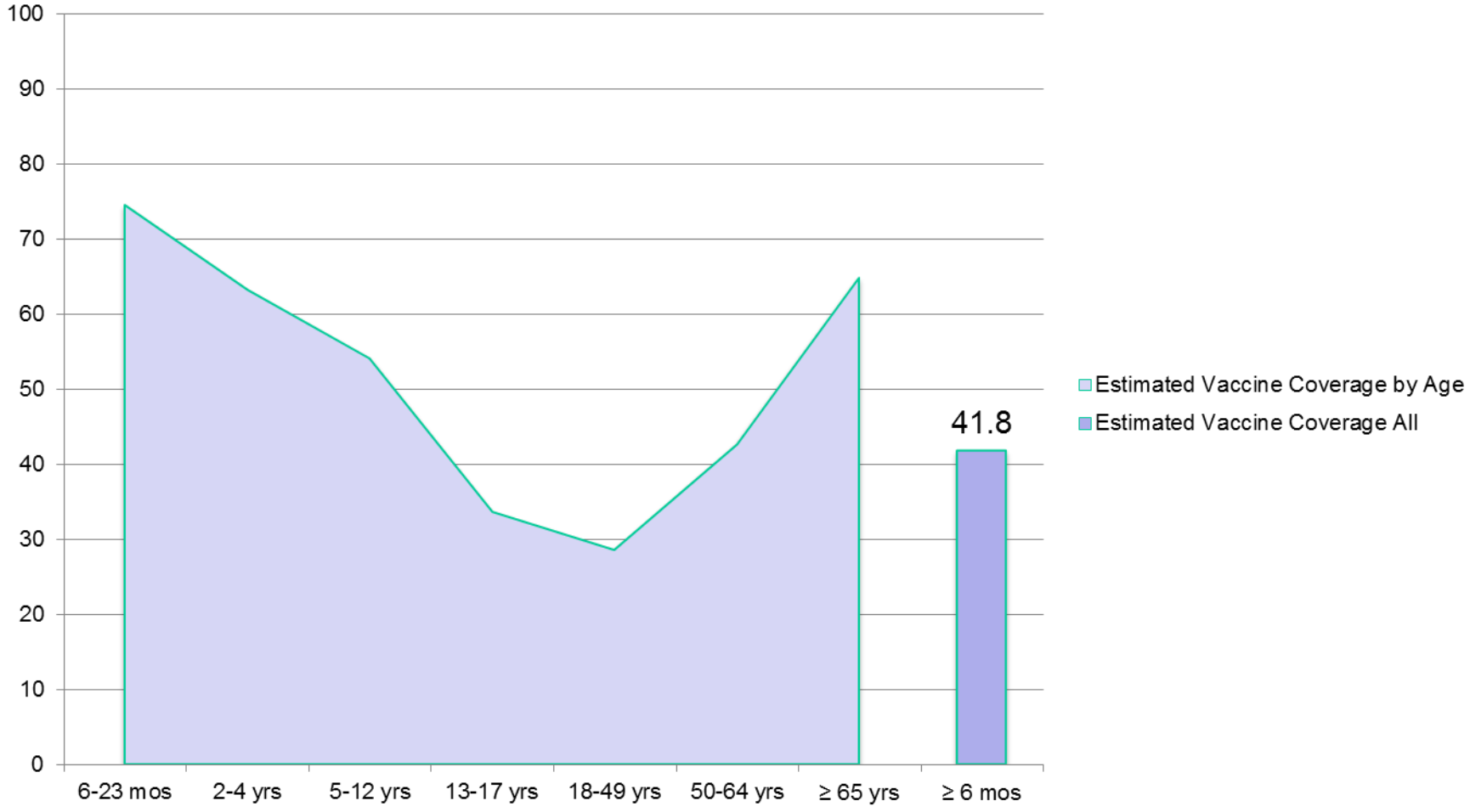
National Immunization Survey Q1/2011-Q4/2011

Flu Vaccination Coverage, United States 2011-12 Influenza Season



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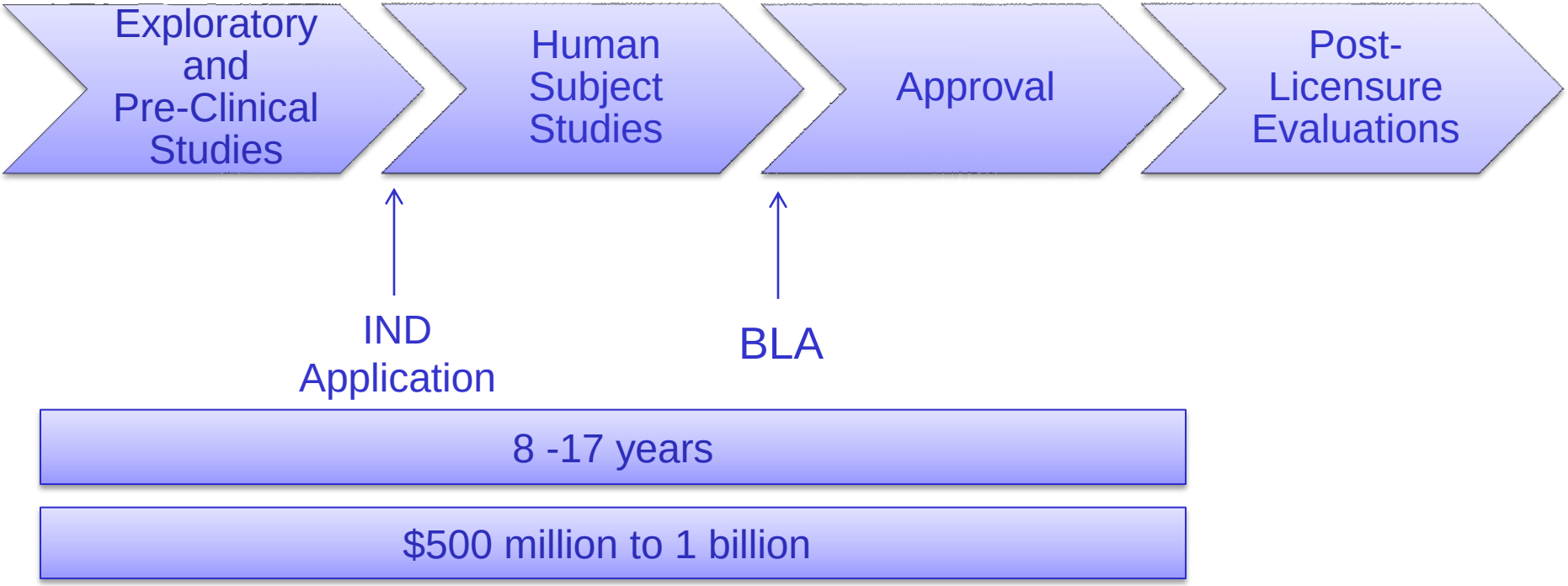
http://www.cdc.gov/flu/professionals/vaccination/coverage_1112estimates.htm

Vaccine Safety is a Prime Consideration in all Stages of Vaccine Development



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Pediatrics 2011;127:s16-22

Pre-Clinical Development

- Develop rationale based on disease
- Identify an immunogen
- Develop manufacturing process
- Preclinical studies
  - Acute toxicity
    - Escalating doses of candidate vaccine administered to animals by the route expected to be used in humans
      - Must include doses higher than those used in humans
      - Helps predict safe starting dose in humans
      - Assess for behavioral changes, injection-site inflammation, and laboratory evaluations
  - In vivo pyrogenicity testing in animals (rabbits and/or guinea pigs)
  - Safety studies (rats or possibly primates)

Pre-licensure Human Subject Studies

Phase	N	Information Obtained
1	20-100	Basic information on safety and tolerability Detects serious common side effects
2	Hundreds	Immunogenicity, dosing (best dose, interval and number of doses), and common side effects
3	Thousands - Tens of Thousands	Evaluate safety and efficacy (surrogates of efficacy) Assesses lot consistency

Monitoring Vaccine Safety in Clinical Trials

- Solicited side effects (time period specified)
  - Immediate hypersensitivity reactions
  - Local injection site reactions
  - Systemic reactions
- Unsolicited side effects (time period specified)
  - Adverse events
  - Serious adverse events
  - Onset of a new chronic medical condition

    (longer follow-up needed)

Local Injection Site Reactions

- Participants / parents rate local site reactions following vaccination using a memory aid
  - Pain – intensity (none, mild, moderate, severe)
  - Tenderness - intensity (none, mild, moderate, severe)
  - Swelling / Induration - intensity (none, mild, moderate, severe)
  - Swelling / Induration – size mm
  - Redness / Erythema - size mm
- Recorded information is obtained from participants / parents during telephone calls and clinic visits

Systemic Reactions

- Daily temperature measurements and rating (none, mild, moderate, severe) of general body symptoms following vaccination using a memory aid
- Age dependent assessments

<u>Adult</u>

- Feverishness
- Fatigue Malaise
- Body aches
- Headache
- Nausea

<u>Young Children</u>

- Irritability
- Decreased appetite
- Lethargy
- Vomiting

- Recorded information is obtained from participants / parents during telephone calls and clinic visits

Adverse Event

- Adverse event – Any undesirable experience associated with the use of a medical product in a patient.
  - Graded for severity or intensity
  - Assessed for relatedness to study product

Serious Adverse Event

- Serious adverse event – an adverse event when the participant or patient outcome was:
  - Death
  - Life-threatening
  - Hospitalization (initial or prolonged)
  - Disability or Permanent Damage
  - Congenital Anomaly/Birth Defect
  - Required Intervention to Prevent Permanent Impairment or Damage (Devices)
  - Other Serious (Important Medical Events)
- Need to be reported to the FDA

Pre-licensure Trial Limitations

- Relatively small size (hundreds to thousands of study participants)
  - May not detect rare side effects
  - Events occurring at a frequency of <1 in 1,000
- Strict inclusion / exclusion criteria
  - AEs affecting certain subpopulations may not be identified
    - Persons with underlying medical conditions
    - Persons taking medications
    - Pregnant women
    - Elderly
- Usually of limited duration
  - Delayed reactions may not be evident

Pre-licensure Trial Limitations – Rotavirus example

- In 1998, a rhesus-based tetravalent rotavirus vaccine (RRV-TV, Rotashield) was licensed and recommended for routine immunization of U.S. infants.
- RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception.
- Pre-licensure trials of current RV1 and RV5 vaccines in over 130,000 participants did not detect an increase risk of intussusception
- Some, but not all, post marketing studies of the currently licensed vaccines have detected a small increased risk for intussusception following rotavirus vaccine administration, particularly during the first week following the first dose of vaccine.

Biologic License Application

Data from Clinical and Laboratory Studies

- Product Safety
- Product Purity
- Product Potency

Good Manufacturing Practice – Regulation Provisions

- Quality control
- Personnel qualifications and responsibilities
- Building and facilities – design, construction, and maintenance
- Equipment – design, construction, cleaning, maintenance
- Components and product containers and closures
- Production and process controls
- Packaging and labeling control
- Holding and distribution
- Laboratory controls
- Records and reports

Post Approval - Manufacture Monitoring

- Lot-release testing
  - Sterility and purity – detects presence of fungal or bacterial contaminants
  - General safety test- detects toxicity (conducted in small animal models)
  - Identity test – verifies product induces antibodies (conducted in small animal models)
  - Potency – verifies immunogenicity, antigen content, or chemical composition
  - Purity – verifies freedom from extraneous materials
  - Tests for removal of process contaminants
  - Pyrogenicity: detects presence of fever-inducing substances
- Monitoring of vaccine and production activities
  - Inspected every 2 years (Yearly for influenza vaccine manufacturers)

Post-licensure Evaluations - Industry

- Phase IV studies to investigate causality of uncommon but potentially vaccine associated AEs that occur among a larger and greater diversity of persons who receive the vaccine after licensure
- FDA licensure may be contingent on these studies
- Pharmacovigilence programs
- Pregnancy registries – monitor outcomes when vaccines are administered to pregnant women

Post Approval Vaccine Safety Evaluation

- VAERS – Vaccine Adverse Events Reporting System
- VSD – Vaccine Safety Datalink
- CISA – Clinical Immunization Safety Assessment
- VAU – Vaccine Analytic Unit
- PRISM - Post-Licensure Rapid Immunization Safety Monitoring

Adverse Events: Causality

- Health problem occurs during a plausible time period following vaccination
- Adverse event corresponds to those previously associated with a particular vaccine
- The event conforms to a specific clinical syndrome whose association with vaccination has a strong biologic plausibility or occurs following natural disease
- A laboratory result confirms the association
- The event recurs on re-administration of vaccine
- A controlled clinical trial demonstrates greater risk of a specific adverse event in those vaccinated when compared to control groups
- A finding linking an adverse event to vaccine has been confirmed in other studies

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Centers For Disease Control And Prevention. Epidemiology And Prevention Of Vaccine-preventable Diseases. Atkinson W, Wolfe S, Hamborsky J, Eds. 12th Ed., Second Printing. Washington DC: Public Health Foundation, 2012.

Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
- Authorized by National Childhood Vaccine Injury Act of 1986
  - Requires health care providers to report adverse events (possible side effects) that occur following vaccination
- Accepts reports from healthcare providers, manufacturers and the public
- Jointly administered by CDC and FDA
- 30,000 reports annually
  - 10-15% are serious (permanent disability, hospitalization, life-threatening illness or death)

http://www.cdc.gov/vaccinesafety/Activities/vaers.html

Objectives of VAERS

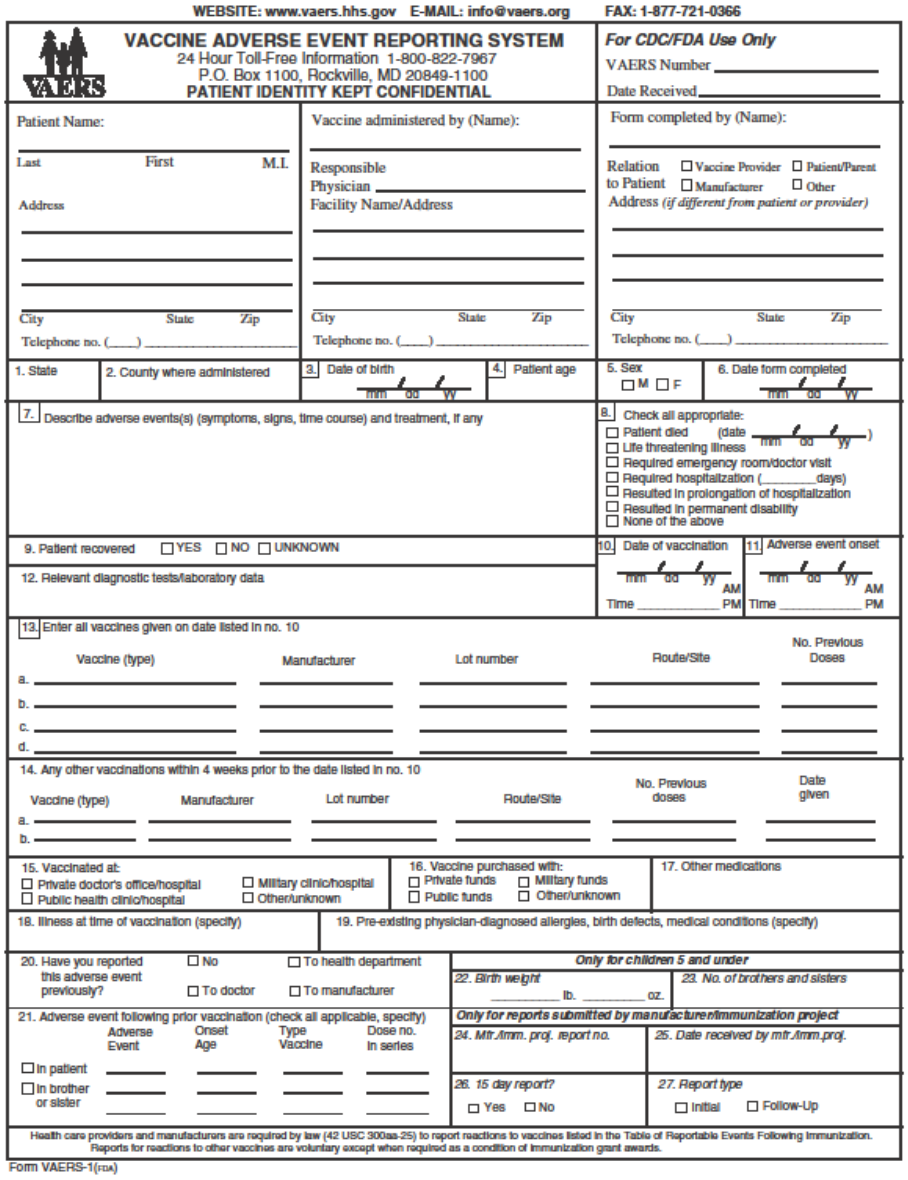
- Signal detection/hypothesis generation
  - Detect new, unusual, or rare vaccine adverse events
  - Monitor increases in known adverse events
  - Identify potential patient risk factors for particular types of adverse events
  - Identify vaccine lots with increased numbers or types of reported adverse events
  - Assess the safety of newly licensed vaccines
- Rapidly respond to vaccine safety concerns or public health emergencies

http://www.cdc.gov/vaccinesafety/Activities/vaers.html

VAERS Form

- Online or paper (mailed or faxed)
- Information collected:
  - The type of vaccine received
  - The timing of the vaccination
  - The onset of the adverse event
  - Current illnesses or medication
  - Past history of adverse events following vaccination
  - Demographic information about the recipient

http://www.cdc.gov/vaccinesafety/Activities/vaers.html



WEBSITE: www.vaers.hhs.gov E-MAIL: info@vaers.org FAX: 1-877-721-0366

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

For CDC/FDA Use Only
VAERS Number
Date Received

Patient Name: Last First M.I.
Address
City State Zip
Telephone no. (___) ___

Vaccine administered by (Name):
Responsible Physician
Facility Name/Address
City State Zip
Telephone no. (___) ___

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (___) ___

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm dd yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (___days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy Time ___ AM PM

11. Adverse event onset mm dd yy Time ___ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight ___ lb. ___ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1(FDA)

http://vaers.hhs.gov/resources/vaers_form.pdf

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Selected VAERS Contributions

- Intussusception among recipients of rotavirus vaccine--United States, 1998-1999. **Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 1999 Jul 16;48(27):577-81**
- Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine--United States, October 2005-February 2006. **Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2006 Apr 7;55(13):364-6.**
- Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. **Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, Markowitz LE, Iskander J. JAMA. 2009 Aug 19;302(7):750-7.**
- Intussusception After Rotavirus Vaccines Reported to US VAERS, 2006-2012. **Haber P, Patel M, Pan Y, Baggs J, Haber M, Museru O, Yue X, Lewis P, Destefano F, Parashar UD. Pediatrics. 2013 Jun;131(6):1042-9.**

Recent VAERS Contribution

- During the 2010-11 influenza season, FDA and CDC detected an increase in the number of reports to VAERS of febrile seizures following TIV vaccination (flu shot) in children younger than 2 years of age
  - Findings served as an indication (signal) that further investigation was warranted

Leroy Z. et al. Vaccine 2012 Mar 2;30(11):2020-3.

VAERS: Strengths and Limitations

Strengths

- National data
- Rapid signal detection
- Can detect rare adverse events (AE)
- Generates hypotheses for further study
- Data are available to the public
  http://vaers.hhs.gov/index

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- **Generally cannot assess if vaccine caused an AE**
- Lack of unvaccinated comparison group

VAERS: Limitations

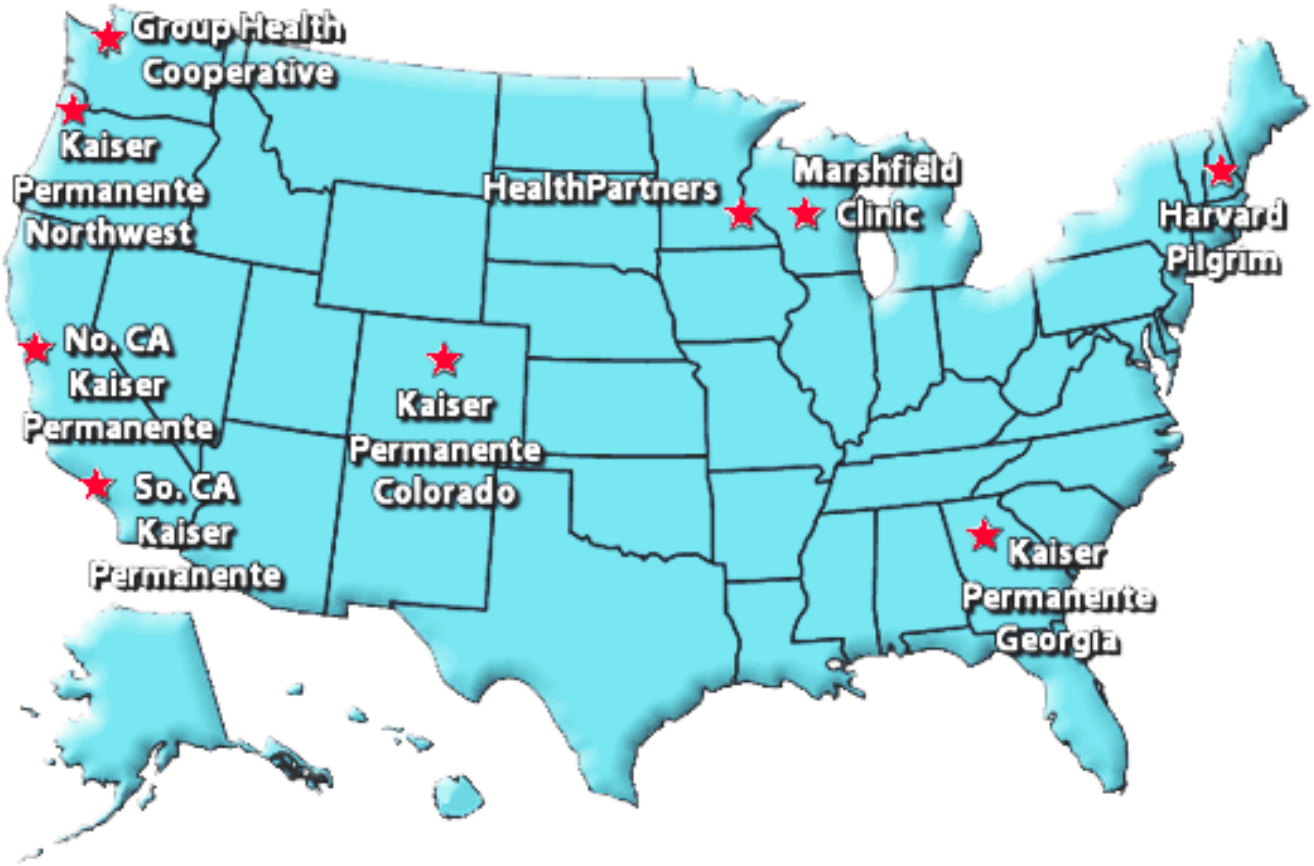
- Adverse events reported to VAERS may or may not be caused by vaccines.
- There are reports in VAERS of common conditions that may occur by chance alone that are found shortly after vaccination.
- Further investigation may find no medical link between vaccination and these conditions.

Vaccine Safety Datalink (VSD)

- Established in 1990 to monitor immunization safety and address the gaps in scientific knowledge about rare and serious events following immunization
- A collaborative project among CDC and nine healthcare organizations (HCOs)
- Data on >9 million persons (with a birth cohort of 95,000 annually)
- Computerized linked immunization and health care databases allow studies to be conducted rapidly and efficiently
- Allows for planned immunization safety studies as well as timely investigation of new safety signals

http://www.cdc.gov/vaccinesafety/activities/vsd.html

VSD Sites



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http://www.cdc.gov/vaccinesafety/activities/vsd.html

VSD Objectives/Strategic Priorities

- Evaluate the safety of newly licensed vaccines
- Evaluate the safety of new vaccine recommendations for existing vaccines
- Evaluate clinical disorders after immunizations
- Assess vaccine safety in special populations at high risk
- Develop and evaluate methodologies for vaccine safety assessment

Baggs J et al. Pediatrics 2011;127;S45

VSD Procedures

- Prepares computerized data files by using a standardized data dictionary containing demographic and medical information on its members, such as age and gender, health plan enrollment, vaccinations, hospitalizations, outpatient clinic visits, emergency department visits, urgent care visits, and mortality data, as well as additional birth information (e.g., birth weight) when available.
- Other information sources, such as medical chart review, member surveys, and pharmacy, laboratory, and radiology data, are often used in VSD studies to validate outcomes and vaccination data

Baggs J et al. Pediatrics 2011;127;S45

VSD Methodology

- Traditional epidemiologic methods
  - Retrospective cohort studies
  - Case-control studies
  - Self-control case series designs
- Rapid Cycle Analysis (RCA)
  - Used to assess the safety of newly licensed vaccines or change in recommendations for current vaccines
  - Adverse events being monitored are pre-specified
  - Observed number of suspected events is compared with the expected number of events
  - Comparisons are conduced weekly to look for safety signals
  - Adverse events can also be added if a signal for an event (not already pre-specified) is identified from another system

Baggs J et al. Pediatrics 2011;127;S45

Selected VSD Contributions

- MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink project. The Vaccine Safety Datalink Team. Davis RL, Marcuse E, Black S, Shinefield H, Givens B, Schwalbe J, Ray P, Thompson RS, Chen R. Pediatrics. 1997 Nov;100(5):767-71
- Childhood vaccinations and risk of asthma. DeStefano F, Gu D, Kramarz P, Truman BI, Iademarco MF, Mullooly JP, Jackson LA, Davis RL, Black SB, Shinefield HR, Marcy SM, Ward JI, Chen RT; Vaccine Safety Datalink Research Group. Pediatr Infect Dis J. 2002 Jun;21(6):498-504.
- Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, Lewis E, Eriksen E, Ray P, Marcy SM, Dunn J, Jackson LA, Lieu TA, Black S, Stewart G, Weintraub ES, Davis RL, DeStefano F; Vaccine Safety Datalink Team. N Engl J Med. 2007 Sep 27;357(13):1281-92
- Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E; Vaccine Safety Datalink. Pediatrics. 2010 Jul;126(1):e1-8

Recent VSD Contribution

- Elevated risk of febrile seizures in young children 0-1 days following 2010-11 trivalent inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine
- Among children 6-59 months of age:
  - The incidence rate ratio (IRR) for TIV adjusted for concomitant PCV13 was 2.4 (95% CI 1.2, 4.7)
  - The IRR for PCV13 adjusted for concomitant TIV was 2.5 (95% CI 1.3, 4.7).
  - The IRR for concomitant TIV and PCV13 was 5.9 (95% CI 3.1, 11.3).
  - Highest risk estimates occurring at 16 months of age

Tse A, et al Vaccine. 2012 Mar 2;30(11):2024-31

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VSD: Limitations

- Limited capability to detect very rare AEFI in minimal time periods
- Accuracy of computerized records to determine medical outcomes varies
  - Need to validate data through medical chart review

http://www.cdc.gov/vaccinesafety/activities/vsd.html

Clinical Immunization Safety Assessment (CISA) Project

- CISA is a national network of vaccine safety experts from the CDC's Immunization Safety Office (ISO), seven medical research centers, and other partners, which provides a comprehensive vaccine safety public health service to the nation
  - Conducts research and reviews clinical cases and issues about vaccine safety

CDC- Centers for Disease Control and Prevention

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Clinical Immunization Safety Assessment (CISA) Project

- **Mission**
  - To improve understanding of adverse events following immunization (AEFI) at the individual-patient level

- **Goals**
  - Serve as a vaccine safety resource for consultation on clinical vaccine safety issues
  - Develop strategies to assess individuals who may be at increased risk for AEFI
  - Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations

CISA Project Sites and Overall Principal Investigators (PI)

- Boston Medical Center, MA
  - PI: Colin D. Marchant, MD
- Cincinnati Children's Hospital Medical Center, OH
  - PI: Steven Black, MD
- Columbia University, NY
  - PI: Dr. Anne Gershon, MD and Philip LaRussa, MD
- Duke Clinical Research Institute, Duke University, NC
  - PI: Emmanuel “Chip” Walter, MD, MPH
- Johns Hopkins University, MD
  - PI: Neal Halsey MD
- Kaiser Permanente Northern California (KPNC), CA
  - PI: Roger Baxter, MD and Nicola Klein, MD, PhD
- Vanderbilt Medical Center, TN
  - PI: Kathryn M. Edwards, MD

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CISA Current Activities

- **Clinical Case Reviews:**
  - Provides a clinical case evaluation service for US healthcare providers who have vaccine safety questions about a specific patient residing in the US
- **Vaccine Safety Issues:**
  - Provides consultation that enhances understanding of vaccine safety issues and informs clinical and public health practices
- **Research:**
  - Conducts clinical research studies that address priority areas for vaccine safety
- **Public Health Response:**
  - Has procedures in place to assist in vaccine safety emergencies in collaboration with other partners

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CISA Clinical Case Reviews

- CISA provides consultation to US healthcare providers who have vaccine safety questions about a specific patient residing in the US if routine guidance* does not address the issue
  - CISA convenes a working group of clinicians with expertise in vaccine safety, including specialists such as neurologists, and allergists/immunologists, to evaluate complex vaccine safety cases
- Not all cases will be selected for a CISA evaluation. Cases not selected for CISA will be referred to the CDC's Immunization Safety Office for a response
- No cost to the provider for a CISA evaluation
- Advice from CISA and CDC is meant to assist in decision making rather than provide direct patient management (which is the responsibility of the treating healthcare provider)

***e.g. Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/acip/**

American Academy of Pediatrics (AAP): http://www2.aap.org/immunization/

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CISA Evaluation for Patient Vaccine Safety Questions

- Procedure for requesting a CISA evaluation:
- Send an email to CISAeval@cdc.gov
  - Provide your name, profession (e.g. MD, DO, NP, PA, RPh), phone number, and email
  - Do NOT include patient names or any other patient identifying information
  - Include the vaccine safety question and pertinent patient information
- Providers will be notified within 1-2 weeks if the case will be reviewed by CISA
- Whether a case is accepted for a CISA consultation or not, it is recommended that the healthcare provider submit a report to the Vaccine Adverse Event Reporting System (VAERS) (vaers.hhs.gov)
- http://www.cdc.gov/vaccinesafety/Activities/CISA.html

CISA Current Studies

- Assessing Fever Rates in Children ages 24 to 59 months after Live Attenuated Influenza Vaccine (LAIV) or Inactivated Influenza Vaccines (IIV) Using Text Messaging for U.S. influenza vaccines in 2012–13 & 2013-2014
  - Lead CISA Site: Columbia University
  - This study is registered at ClinicalTrials.gov

- Pilot Study to Assess Flares Following Inactivated Influenza Vaccine in Children with Systemic Lupus Erythematosus (SLE)
  - Lead CISA Site: Vanderbilt University, with subcontract to the Baylor Institute for Immunology Research (BIIR)

Selected CISA Contributions

- Recurrent Guillain-Barre syndrome following vaccination. Baxter R, Lewis N, Bakshi N, Vellozzi C, Klein NP; CISA Network. Clin Infect Dis. 2012 Mar;54(6):800-4.
- Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009. Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, LaRussa PS, Sparks RC, Tokars JI, Pahud BA, Aukes L, Jakob K, Coronel S, Choi H, Slade BA, Edwards KM. Vaccine. 2011 Sep 16;29(40):6920-7.
- An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, Halsey NA; Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network. Pediatrics. 2008 Sep;122(3):e771-7.

Clinical Immunization Safety Assessment (CISA) Project Research

Strengths

- Can implement prospective, multi-site clinical studies (hundreds of subjects)
- Expertise in vaccine safety and many clinical areas, including ob/gyn
- Access to patients receiving vaccines, including special populations
- Can collect detailed clinical data on patients and biological specimens
- Ability to recruit controls

Limitations

- Sample size limited to study rare adverse events
- Potential challenges to recruit and retain subjects
- May not have access to vaccine records for vaccines given outside site
- Potential for lack of geographic or race/ethnicity diversity
- Clinical studies may be labor and resource-intensive

ISO Scientific Agenda: Research Needs Covered in Ongoing or Potential Future CISA Studies*

- Vaccine safety in persons with autoimmune diseases
- Vaccine safety in pregnant women
- Safety of annual influenza vaccination for children and adolescents
- Clinically important outcomes associated with fever after vaccination

***ISO Scientific Agenda, Research Needs,**
http://www.cdc.gov/vaccinesafety/00_pdf/ISO-Final-Scientific_Agenda-Nov-10.pdf

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Vaccine Analytic Unit (VAU)

- Established in 2003 to monitor longer term safety of vaccines administered to young adults of military age
- A collaborative project between CDC and DOD with input from the FDA
- Uses data from the defense medical surveillance system
- Agenda
  - Investigation of AVA adverse events
  - Investigation of 2009 H1N1 vaccine
  - Investigations of yellow fever, smallpox, and Japanese encephalitis vaccines

http://www.cdc.gov/vaccinesafety/activities/vsd.html

Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Established in 2009
- Funded by the FDA and coordinated by the National Vaccine Program Office in collaboration with America's Health Insurance Plan, Harvard, and the CDC
- Uses data from national health insurance plans and immunization registries to evaluate vaccine safety issues
  - Large populations - 25 million
- Used to evaluate 2009 H1N1 vaccine safety
  - 2009 H1N1 and Guillain Barré Syndrome
  - Febrile seizure risk after PCV13 and IIV
  - Intussusception following RV
  - Venous thromboembolism following HPV

http://www.cdc.gov/vaccinesafety/activities/vsd.html

Brighton Collaboration

- International organization launched in 2000
- Facilitates the development, evaluation, and dissemination of high-quality information about the safety of vaccines
- Primary objective is to develop standardized definitions of adverse events following immunization (AEFI)
  - Definitions for common AEFI (e.g. fatigue and fever), and uncommon AEFI (e.g. hypotonic hypo-responsive episodes and acute disseminated encephalomyelitis)
- Develops guidelines for the collection, analysis and presentation of data in pre- and post- licensure studies

Institute of Medicine (IOM) Reviews

- The Institute of Medicine (IOM) is an independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public
- Established in 1970, the IOM is the health arm of the National Academy of Sciences
- Aim is to help those in government and the private sector make informed health decisions by providing evidence upon which they can rely

http://www.iom.edu/

IOM 2013 - Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies

"The IOM committee uncovered no evidence of major safety concerns associated with adherence to the childhood immunization schedule. Should signals arise that there may be need for investigation, however, the report offers a framework for conducting safety research using existing or new data collection systems"

http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx

IOM 2011 - Adverse Effects of Vaccines: Evidence and Causality

"The committee finds that evidence convincingly supports a causal relationship between some vaccines and some adverse events—such as MMR, varicella zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines linked to anaphylaxis. Additionally, evidence favors rejection of five vaccine-adverse event relationships, including MMR vaccine and autism and inactivated influenza vaccine and asthma episodes. However, for the majority of cases (135 vaccine-adverse event pairs), the evidence was inadequate to accept or reject a causal relationship. Overall, the committee concludes that few health problems are caused by or clearly associated with vaccines."

http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx